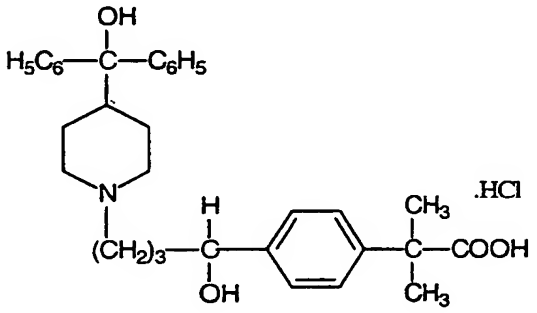
AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

FIELD OF THE INVENTION

This invention relates to an amorphous form of fexofenadine hydrochloride, to a process for the preparation thereof, and to a composition containing it.

BACKGROUND OF THE INVENTION

Chemically, fexofenadine is 4-[4-[4-hdroxydiphenylmethyl)-1-piperidinyl]-hydroxybutyl]-α, α-dimethylbenzene acetic acid also known as terfenadine carboxylic acid metabolite having the Formula I.



Formula I

Fexofenadine hydrochloride (Terfenadine carboxylic acid hydrochloride) is an effective antihistamine which avoids adverse effects associated with the administration of terfenadine including abnormal heart rhythms in some

patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin.

The pharmaceutical industry has, of late, conducted studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, crystalline/liquid crystalline/non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials tranquilizers etc, exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. It has also been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form [Konne T., Chem. Pharm. Bull. 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is a good example of an amorphous form exhibiting higher bioavailability than the crystalline form. Sertraline, Frentizole, Sulphathiazole, Indomethacine, etc., are some of the important examples of pharmaceuticals which exhibit polymorphism. A number of patents have been granted pertaining to these new forms of old drugs. To cite a few, US Patent No. 5,248,699 discloses five polymorphic forms of sertraline hydrochloride while EP 014490 describes four polymorphic forms of Frentizole. EP 490648 and EP 022527 also deal with the subject of polymorphism in drugs.

PCT patent application WO 95/31437 discloses fexofenadine hydrochloride in various new crystalline forms designated Form I, Form II and Form IV and methods for their preparation.

SUMMARY OF THE INVENTION

The first object of the present invention is to provide fexofenadine hydrochloride in an amorphous form. The amorphous form of fexofenadine hydrochloride is prepared by an efficient process which uses conditions which are convenient to operate on a commercial scale and operationally safe.

The second object of the present invention is to provide a process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering amorphous form of fexofenadine hydrochloride from the solution thereof by spray drying or freeze drying technique.

In yet another aspect of this invention, there is provided a pharmaceutical composition comprising fexofenadine hydrochloride in an amorphous form with one or more pharmaceutical carriers and/or excipients.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a freeze drying

technique. The freeze dryer (Model : Virtis Genesis SQ Freeze – Dryer), which is used, operates on the principle of lyophilization, i.e., a process of stabilizing initially wet materials (aqueous solution or suspensions) by freezing them, then subliming the ice while simultaneously desorbing some of the bound moisture (primary drying). Following disappearance of the ice, desorption may be prolonged (secondary drying). This process is preferably conducted under vacuum.

In a more preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a spray drying technique. The Mini-Spray Dryer (Model : Buchi 190, Switzerland) which is used, operates on the principle of nozzle spraying in a parallel – flow, i.e., the sprayed product and the drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, argon and carbon dioxide. Nitrogen is preferred in this case.

The term "suitable solvent" means lower alkanol or combination of lower alkanol, ester, ketone, chlorinated solvent and mixture (s) thereof. Lower alkanol includes those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, amyl alcohol and t-butanol. The term ketone or ester includes solvents having from one to ten carbon atoms such as acetone, methyl ethyl ketone, 2-butanone, 4-methylpentan-2-one, ethyl acetate or n-butylacetate. The suitable chlorinated

solvents include dichloromethane, chloroform or carbon tetrachloride. Mixture of these solvents are also contemplated.

Amorphous fexofenadine hydrochloride prepared according to the process of the present invention may be characterized by its infra-red spectrum in KBr disc (Figure 1) and by its X-ray powder diffraction pattern (Figure 2). The infra red spectrum in KBr (Figure 1) obtained for the samples prepared by the process of the present invention is different than infra red spectrum in KBr for crystalline form (Figure 3) of fexofenadine hydrochloride obtained per WO patent application (WO 95/31437). X-ray powder diffraction patterns gave a plain halo (Figure 2) and show no peaks which are characteristic of a crystalline fexofenadine hydrochloride (Figure 4) thus demonstrating the amorphous nature of the product.

The present invention is illustrated by the following examples which are not intended to limit the effective scope of the claims.

Preparation of amorphous fexofenadine hydrochloride by Spray Drying using crystalline fexofenadine hydrochloride

EXAMPLE 1

Fexofenadine hydrochloride crystalline (124g, 0.231 moles) was dissolved in methanol (300ml) at 25-30ºC. The clear solution so obtained was subjected to spray drying in a Mini-Spray Dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (114g).

X-ray powder diffraction pattern (Figure 2) shows a plain halo thus demonstrating the amorphous nature of the product. Infrared spectrum in KBr (Figure 1) is different than the one obtained for crystalline form of fexofenadine hydrochloride (Figure 3).

EXAMPLE 2

The process of Example 1 was repeated with fexofenadine hydrochloride (10g, 0.0186moles) using ethylacetate (20ml) and methanol (20ml) instead of methanol to give amorphous fexofenadine hydrochloride (9.2g). IR (KBr) spectrum and x-ray crystallography confirmed that the material was amorphous in nature.

EXAMPLE 3

The process of Example 1 was repeated with fexofenadine hydrochloride (10g, 0.0186 moles) using acetone (20ml) and methanol (20ml) instead of methanol to give amorphous fexofenadine hydrochloride (8.9g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.

Preparation of amorphous fexofenadine hydrochloride by spray drying using fexofenadine base.

EXAMPLE 4

Fexofenadine (15gm, 0.0299 moles) was suspended in methanol (60 ml) and to it was added isopropanol containing equivalent molar hydrogen

chloride to get a clear solution. The clear solution was subjected to spray drying in a mini spray dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (14.9g). IR (KBr) and x-ray crystallography revealed that the product was amorphous.

EXAMPLE 5

The process of Example 4 was repeated with fexofenadine (10g, 0.0199 moles) using methanol (40ml) and to it was added methanol containing equimolar hydrogen chloride to give amorphous fexofenadine hydrochloride (9.5g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.